Current Neurology and Neuroscience Reports
https://doi.org/10.1007/s11910-024-01383-6

REVIEW

Sedation Vacations in Neurocritical Care: Friend or Foe?

Juan Sebastián Reyes-Bello[1] · **Luis Rafael Moscote-Salazar**[1,3] · **Tariq Janjua**[2]

Accepted: 20 September 2024
© The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature 2024

Abstract

Purpose of Review To evaluate the role of sedation vacations in optimizing patient outcomes and enhancing the quality of care in neurological intensive care units (ICUs). We discuss the importance of sedation management in neurocritical care, considering recent research findings and clinical guidelines.

Recent Findings Recent studies have highlighted the significance of sedation interruption protocols in improving patient outcomes in the ICU setting. Evidence suggests that daily sedation interruptions can reduce the duration of mechanical ventilation, ICU length of stay, and mortality rates. However, the implementation of these protocols requires careful consideration of patient-specific factors and a multidisciplinary approach.

Summary Sedation vacations play a critical role in neurocritical care by reducing mechanical ventilation duration, ICU stay length, and mortality rates. Despite the benefits, the presence of complications must be addressed to avoid adverse outcomes. Continued research is necessary to refine these strategies and improve guideline quality, ensuring safe and effective sedation management in critically ill neurological patients.

Keywords Neurocritical care · Mechanical ventilation · Sedation vacations · Outcomes · Mortality · Brain traumatic injury

Abbreviations

ARDS	Acute respiratory distress syndrome
TBI	Traumatic Brain Injury
BIS	Bispectral Index
BBB	Blood Brain Barrier
CMRO2	Cerebral metabolic rate of oxygen
CBF	Cerebral blood flow
CPP	Cerebral perfusion pressure
DAMPs	Damage Associated Molecular Patterns
GS	Glymphatic System
GFAP	Glial Fibrillary Acid Protein
ICUs	Intensive Care Units
ICP	Intracranial Pressure
MAP	Mean arterial pressure
MV	Mechanical Ventilation
NPE	Neurogenic Pulmonary Edema
PTSD	Post-traumatic stress disorder
PUD	Peptic Ulcer disease
RAGE	Receptor of Advanced Glycation End-Products
RASS	Richmond Agitation-Sedation Scale
RSS	Ramsay Sedation Scale
Scale	Sedation Agitation Scale
SBT	Spontaneous breathing trial
SAH	Subarachnoid Hemorrhage
VAP	Ventilator-Associated Pneumonia

✉ Juan Sebastián Reyes-Bello
jureyesbe@unisanitas.edu.co

✉ Luis Rafael Moscote-Salazar
rafaelmoscote21@gmail.com

✉ Tariq Janjua
icumd@outlook.com

[1] Department of Research, Colombian Clinical Research Group in Neurocritical Care, Bogotá, Colombia

[2] Department of Neurology, Regions Hospital, Saint Paul, MN, USA

[3] AV HealthCare Innovators, LLC, Madison, Wisconsin, USA

Introduction

Intensive care units (ICUs) are staffed by specialized individuals with expertise in treating patients with critical conditions that require concentrated and prompt care [1]. The efficient optimized setup and architecture of this system are directly related to patient safety, especially in the trauma setting [2]. Despite medical efforts, ICU mortality rates remain high and are considered a major clinical endpoint [3]. The most common causes of death are sepsis, severe trauma [4], and multiple organ dysfunction syndrome.

Published online: 01 October 2024

SHOUT
SHARE
IT

Central nervous system and cardiovascular system failure are the most common risk factors [5]. Roughly, 33% of admissions are due to respiratory failure, and most of them end up requiring mechanical ventilatory support [1]. Due to this, many ICUs have established a bundle of daily interventions including a sedation vacation, spontaneous breathing trial (SBT), prophylaxis for deep vein thrombosis, head of the bed 30°, and prophylaxis of peptic ulcer disease (PUD). These are designed to decrease complications derived from patient-ventilator desynchrony such as anxiety, pain, ventilator-associated pneumonia (VAP), and body stress which increases oxygen consumption [6]. Sedation refers to the administration of medications to induce a state of calmness, relaxation, and sometimes unconsciousness in critically ill patients. Several medications can be used to initiate or maintain sedation (benzodiazepines, opioid analgesics, ketamine, dexmedetomidine, propofol, among others), and the decision of which sedative to use should be oriented towards weighing the risk/benefit profile of each specific agent [1, 7].

For many years there was the misconception that patients should be deeply sedated, however, current practices have demonstrated that the excessive use of sedation is dangerous and can lead to detrimental outcomes [7] such as total prolonged intubation and increased length of the ICU stay [1]. Additionally, sedation can also limit the ability to assess the mental status of the patient properly, increasing the risk of delirium, and suppressed brainwave function seen on EEG which has been demonstrated to be associated with the 6-month mortality rates [1]. Sedation vacations were first studied by J.P. Kress et al. in 2000 [8] to highlight the necessity of weaning patients from mechanical ventilation by demonstrating that an interrupted sedation regimen decreased time to extubating by 2 days and reduced the total admission time in the ICU [1, 8].

The understanding of neurophysiology and the compensatory mechanisms in patients with acute neurological damage is essential to offer a specialized approach tailored to critical care, especially in terms of sedation and analgesia. This review aims to evaluate the role of sedation vacations in optimizing patient outcomes and enhancing the quality of care in the neurological intensive care unit setting.

Pathophysiology of Acute Neurological Damage

After a neurological injury, the brain parenchyma changes, and physiological responses secondary to compressive and vascular damage can be variable in a time-dependent manner after the lesion has developed. Within the first 48 h, there is a CSF hypersecretion that stimulates the migration of inflammatory cells and immune mediators produced by glial cells such as cytokines IL-1β, IL-6, MIP-1α, TNF-α, reactive oxygen/nitrogen species, and anti-inflammatory moderators like IL-10, IL 4 simultaneously [9, 10]. Other substances produced secondary to brain aggression have been studied recently. The S100B is a calcium-binding protein expressed by astrocytes that can interact with pattern-recognition receptors like the receptor of advanced glycation end-products (RAGE) and perpetuate the cycle of inflammation causing more damage [11]. Similarly to S100B, molecules such as glial fibrillary acid protein (GFAP), Ubiquitin carboxy-terminal hydrolase L1 (UCH-L1), Tau, and neurofilament light (NF-L) are being studied as potential biomarkers associated with poorer outcomes in patients with brain trauma [12].

To regulate these inflammatory mediators, the glymphatic system (GS) plays a pivotal role as a clearance network. The GS is constituted by five functional compartments: the choroid plexus where the CSF is produced, the perivascular space that serves as a pathway for CSF flow from the subarachnoid space into the brain tissue, the periarterial space that moves content through aquaporin-4 channels (AQP4), the perivenous space and the meningeal and cervical lymphatic vessels as the last pathway before the flow drains out of the brain [10, 13]. When the GS is compromised after an injury, the period of stress and neuroinflammation is prolonged [13]. The AQP4 channel dysfunction can cause a reduction of solute clearance in association with increased ionic and osmotic blood–brain barrier (BBB) permeability exacerbating edema and decreasing depuration [13, 14].

The neuroinflammatory environment can lead to multisystemic damage and dysfunction of peripheral extracranial organs [15]. The lungs appear to be the most sensitive organ to the inflammatory cascade as there is a secondary increase of pulmonary vascular permeability, and about 20% to 30% of patients develop lung injury called neurogenic pulmonary edema (NPE) [15, 16]. Recent studies have demonstrated that there is an inextricable relationship between brain-lung, and gut-lung that can regulate the physiological response after an insult is produced [16, 17]. To better understand, this association has been described as a "triple hit" hypothesis that is constituted by three consecutive events: the sympathetic hyperreactivity secondary to the brain trauma that causes inflammation and oxidative stress ("first hit"), the lung injury derived from that intense reaction ("second hit"), and the hormonal symbiotic role of gut microbiota that regulates the immune, hormonal and metabolic response in the lung microbiome ("third hit') [18]. The central focal reason is considered to be massive central adrenergic firing leading to systemic impact (Fig. 1). This leads to increased pulmonary arterial pressure, marked capillary pressure, and fluid leakage into alveolar space. Contrary to the concept of the peripheral release of catecholamines, the central response to acute neurological injury does not lead to higher systemic blood pressure. Experiments in lung denervation showed

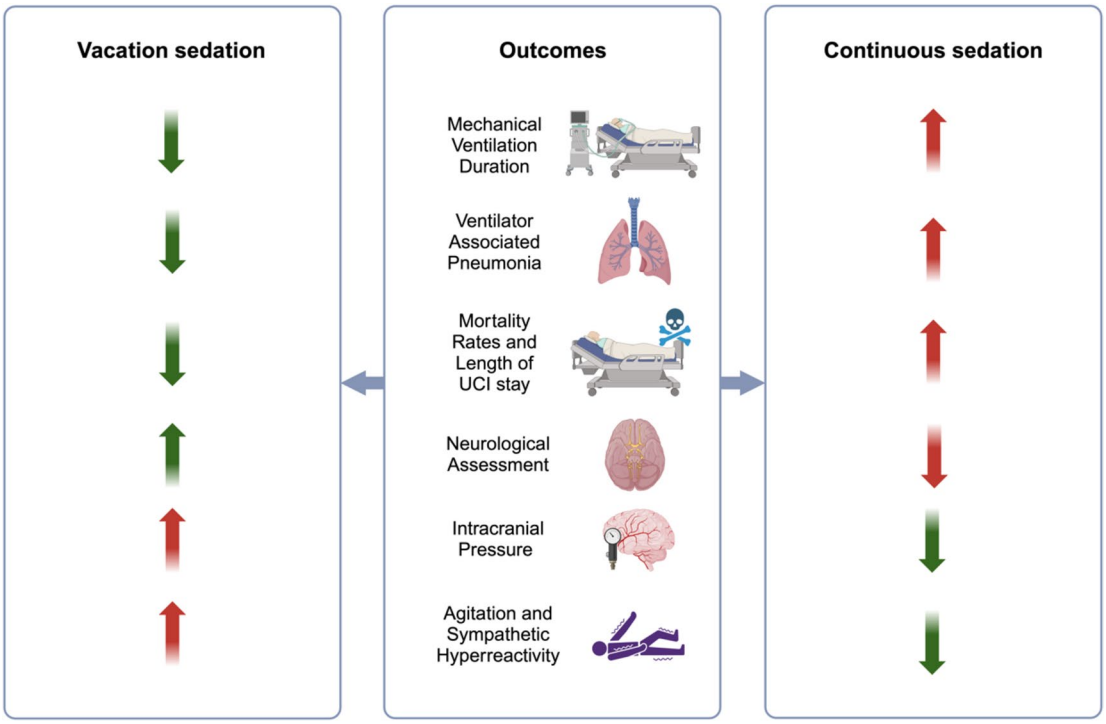

Fig. 1 Balancing risk and benefits of sedation vacations in neurocritical care units

that neural-induced alterations in pulmonary hemodynamics led to an increase in pulmonary vascular permeability.

The gut microbiota dysbiosis can perpetuate respiratory diseases, but the exact mechanism remains unclear. It is thought that the gut-lung axis is interconnected via direct and indirect pathways by the immune response produced secondary to inflammatory triggers. Peptidoglycans and lipopolysaccharides prompt an immune response, the catecholamine storm influences the lung bacterial population like Pseudomonas aeruginosa and Streptococcus pneumonia, and the gut barrier disruption with microbial metabolites that can migrate through the bloodstream and cause bacterial translocation [16, 18]. Critically ill patients have increased gut permeability which makes them susceptible to lung compromise as luminal components from the small intestine such as bacteria, pro-inflammatory cytokines, and bacteria toxins can reach the lungs exacerbating alveolar inflammation and lung injury via the portal circulation or mesenteric lymph vessels [16, 19].

Recent studies have demonstrated the implications of brain trauma over the development of lung inflammation and acute respiratory distress syndrome. Siwicka-Gieroba D. et al. found a considerable concentration of certain apoptotic factors in the bronchoalveolar lavage fluid in patients who suffered severe brain trauma injury (p-value < 0.001) [20]. The study included 40 patients who were followed at different stages: at admission, on day 3, and 7 after admission to the ICU. It was concluded that high levels of those apoptotic factors indicate an activated process of destruction and apoptosis in the respiratory tissue over external, internal, and oxidative stress pathways due to brain trauma. This reaction is capable of influencing the mechanics of the respiratory system by elevating elastance and airway resistance, increasing pulmonary hydrostatic pressures and endothelial permeability which triggers lung inflammation [20].

There is also an interaction between the gut microbiome and the brain. When the microbiome is altered by external factors, the immunoregulatory properties of some metabolites are affected due to a decrease in their production in the gut [21]. Benakis C. et al. demonstrated that following a stroke this dysbiosis leads to a decrease in beneficial bacterial strains, such as those producing short-chain fatty acids, and a subsequent increase in inflammatory cytokines such as IL-17 and a reduction of regulatory T cells [21, 22].

In terms of acute traumatic brain injury (TBI), the release of damage-associated molecular patterns (DAMPs), cytokines, and other immune cells trigger a sympathetic reaction through autonomic neuronal fibers that change the brain's neuroendocrine control of the gut [23]. Thus, the release of neurotransmitters such as acetylcholine and corticotropin-releasing hormone (CRH) is affected, and therefore their regulatory function regarding contractility, secretion of digestive enzymes, serotonin, GABA, dopamine, and other metabolite production associated with neuronal health and blood–brain-barrier integrity is compromised [23].

This cycle of proinflammatory production is enhanced by the compromise in the integrity of the gut, which releases endotoxins from gram-negative bacteria and leads to the activation of macrophages and neutrophils that can migrate to brain tissue and delay recovery [23].

The Impact of Neurocritical Care Units

A neurocritical care unit is composed of physicians, nurses, respiratory therapists, and other health care professionals with expertise in treating patients with life-threatening neurological conditions, postoperative neurosurgical complications, and neurological manifestations of systemic illnesses [24]. The necessity of providing specialized treatment stems from the high mortality rates derived from acute neurological deterioration in conditions such as status epilepticus, massive cerebral infarction, subarachnoid hemorrhage (SAH), intracerebral hemorrhage, and TBI where mortality rates can rise over 50% [24, 25].

Several studies have demonstrated that the presence of a team with specialized training led by neurointensivists decreases mortality and improves outcomes with decreased length of stay,reduction of the reintervention rates for post-operative neurosurgical patients, and cost savings [24, 26]. Finley et al. studied the role of neurocritical care specialists within the ICUs. A hundred eighty-nine patients were included and followed up for 6 months while they were assessed by the modified Rankin scale (mRS) [26]. It was found that compared with other providers (registered nurses, medical intensive care unit professionals, and residents), neurocritical care specialists expected better and worse outcomes with more precision ($P < 0.001$) (96% [95% confidence interval [CI] 89–99%]) [26]. Additionally, a meta-analysis of mortality outcomes was developed by Pham X. et al. and showed a 17% relative risk reduction in patients who received subspecialized care (RR, 0.83; 95% CI, 0.75–0.92; $P = 0.001$) [27]. These findings are significant as patients with delayed transfer from the emergency room to the neurocritical care unit have been associated with poorer prognosis [24].

Sedation Protocols in Neurocritical Care

Sedation protocols aim to guarantee patient comfort, ease necessary medical procedures, and optimize results by controlling agitation, pain, and physiological responses that could aggravate neurological injury. In acute neurological damage, intracranial cerebral pressure (ICP) is a critical parameter that can estimate the cerebrovascular autoregulatory status by reflecting the balance between the generation and drainage of CSF, as well as the volume of the brain parenchyma and blood within the cranial space. ICP monitoring is critical in the treatment of neurological conditions [28]. It functions as an alert system of hostile brain stimuli derived from conditions like brain herniation and expanding intracranial brain lesions where the rise of ICP can limit nutrient delivery to the brain [29].

By initiating sedation in cases with neurological injury, ICP increases can be avoided through different pharmacological mechanisms [29] including the decline in the brain's metabolic demand for oxygen and glucose which in consequence can reduce cerebrovascular circulation dropping cerebral volume and ICP [29, 30]. Furthermore, inhibition of cough and other autonomic reflexes after sedation can decrease the intrathoracic pressure changes and thereby ICP [29].

Clinicians should personalize pharmacotherapy in the neurocritical care setting by considering multiple factors like age, as well as clinical and pharmacological background [31].

Therefore, the pharmacotherapeutic options for sedation used in neurocritical care vary according to the specific aims to achieve in each case and the clinical setting, with some of them used for longer intervals as treatment for status epilepticus unresponsive to antiepileptic agents, paroxysmal sympathetic activity, targeted temperature control, or refractory intracranial hypertension as opposed to short period protocols when prompt awakening is important [1, 32–52] (Table 1).

It is worth mentioning recent findings regarding specific pharmacological agents and their function in distinct neurocritical conditions. Prospective randomized trials have shown better post-operative neurocognitive function in subjects with aneurysmal subarachnoid hemorrhage who were sedated with propofol versus desflurane one month after surgery, still, this finding was not statistically significant ($P = 0.79$) [36]. Furthermore, observational studies discovered that severe traumatic brain injury demanded significantly reduced propofol dose for induction of anesthesia compared to those with mild TBI [37], which if continued can increase the hazard of propofol-related infusion syndrome [38]. A multicentre, retrospective study evidenced that midazolam and propofol were the first line option for early sedation in brain traumatic injuries with lower injury severity scores in the propofol cohort ($P = 0.001$) but no independent associated mortality at 60 days [39].

Regarding refractory status epilepticus, a cohort study developed by Wei-Ting C. et al. showed that midazolam and propofol are alike efficacious for refractory status epilepticus [42].

Later, Liu S. et al. conducted a retrospective cohort study to estimate the early sedation patterns along with the association of dexmedetomidine exposure in cases with moderate-severe traumatic brain injury who were under mechanical ventilation. Compared to unexposed cases, early dexmedetomidine exposure did not significantly ameliorate the 6-month Glasgow outcome scale

Table 1 Pharmacological features of sedatives in neurocritical care

Agent	Features	Recommendations	Recent findings
Propofol	↓ ICP, $CMRO_2$, CMR_{gluc} and CBF Hemodynamic instability (MAP ↓ CPP↓) ↑ Risk of Propofol Infusion Syndrome and hypertriglyceridemia.[32]	Primary sedative for treating intracranial hypertension, status epilepticus that doesn't respond to antiepileptic drugsn and after cardiac arrest when quick awakening is crucial.[32,34]	↑ Postoperative neurocognitive function in patients with aneurysmal subarachnoid hemorrhage.[36] ↓ Induction dose for patients with severe vs mild TBI.[37] ↓ Injury severity scores compared with midazolam use.[39] CSF propofol levels did not match the administered concentration, yet the clinical anesthetic effect was satisfactory.[40]
Midazolam	Hemodynamic stability, amnesic and anticonvulsive effect. [32] ↑ MV duration, ICU length of stay, risk of accumulation, delirium and PSTD. [32, 42]	Secondary sedative, added when other sedatives are inadequate or at their maximum dose.[32] Preffered for hemodynamically unstable patients.[32]	Preliminary evidence indicates that intranasal administration is safe.[41] Midazolam is equally effective as propofol in treating refractory status epilepticus.[42]
Barbiturates	↓↓ ICP, MAP, CPP, $CMRO_2$, CMR_{gluc} and CBF. [32,43] ↑ Adrenal dysfunction, Immunosuppression, Nephrotoxicity, and hepatotoxicity. [32,44]	Rescue treatment for intracranial hypertension and refractory or super-refractory status epilepticus. [32, 43,44]	Current guidelines still recommend limiting their use to refractory cases only due to their secondary effects.[43,44]
Opioids	No ICP- lowering effect, ↑ Risk of accumulation and hyperalgesia dependence. [32]	Pain management for patients under mechanical ventilation. [44]	In patients with aneurysmal subarachnoid hemorrhage-associated headaches an increased opioid dose did not correlate with a greater reduction in assessed pain scores.[45]
Dexmedetomidine	Analgesic and anxiolytic effect with short-acting onset. [32] ↓ risk of respiratory depression and delirium. [46]	Mild sedation for agitation when weaning off other sedatives.[34]	↓ disability rating scale (DRS) scores For patients needing ICP monitoring within the first 24 h of admission, early dexmedetomidine was associated with a higher 6-month GOS-E score, a lower DRS score, and a reduced hospital stay.[46]
Ketamine	No effect on ICP, Hemodinamic stability, ↓ risk of respiratory depression and rapid onset-offset. [32,47,48] ↑ neuroprotection. [50]	Management of refractory or super-refractory status epilepticus when first line agents are ineffective. [34,47]	Continuous infusion is effective in managing refractory seizures and does not suppress respiratory drive.[47,48] There is no association between ketamine and peri-intubation hypoxemia or hemodynamic instability in children with TBI.[49] Provide neuroprotection by reducing cerebral ischemia through its analgesic, anti-inflammatory, sympathomimetic, anti-seizure, and sedative properties.[50]
Volatile anesthetics	Faster extubation, minimal drug interactions, anti-inflammatory, lung protective, reduce blood pressure. [52] No benefit in ICU length of stay. [52]	Short term postoperative, prolonged sedation during mechanical ventilation, status asthmaticus, status epilepticus, ARDS, and COVID-19. [52]	Isoflurane sedation does not adversely affect ICP or cerebral oxygenation in poor-grade aneurysmal subarachnoid hemorrhage patients. However, its significant impact on reducing CPP could restrict the use of volatile agents in situations of hemodynamic instability or high vasopressor requirements.[51]

Pharmacological features of sedatives in neurocritical care

ARDS Acute respiratory distress syndrome, *$CMRO_2$* Cerebral metabolic rate of oxygen, *CMR_{gluc}* Cerebral metabolic rate of glucose, *ICP* Intracranial pressure, *CBF* Cerebral blood flow, *CPP* Cerebral perfusion pressure, *MAP* Mean arterial pressure, *MV* Mechanical Ventilation, *PTSD* Post-traumatic stress disorder, *ICU* Intensive care unit

extended (GOS-E) score (OR = 1.48; 95% CI, 0.98–2.25), but it was linked to a lower Disability rating scale (DRS) (OR = -3.04; 95% CI, -5.88 to -0.21) [46]. For cases demanding ICP monitoring within the first 24 h of admission, early dexmedetomidine was associated with an increased 6-month GOS-E score (OR = 2.17; 95% CI, 1.24–3.80), a lower DRS score (mean difference, -5.81; 95% CI, -9.38 to -2.25), and a reduced hospitalization length (HR = 1.50; 95% CI, 1.02–2.20) [46].

Understanding the pharmacological features of various agents is vital to determining the ideal option for critical cases. Other recent medication-related data is exposed in Table 1.

Clinical neurological examination in neurocritical care is essential to establish appropriate treatments as these patterns of clinical features are distinct enough to guide practice choices [53]. In fact, studies have demonstrated that autonomous reflexes like pupillary dilation could help assess the need for analgesia before potentially painful interventions [54, 55]. When it comes to prognostic and mortality rates, the COVID-19 infection served as an apparent setting where cases with clinical and neurophysiologic cerebral dysfunction had the worst results associated with delayed awakening, delirium, and 28-day mortality [56]. Despite sedation protocols avoiding the exacerbation of neurological injuries, detection of neurological deterioration in patients under sedation is imperative. For this reason, it is essential to avoid excessive sedation, titrate to treatment targets, stop administration as soon as the indication is no longer present, and supervise precisely during titration [1, 32–52].

Neurological evaluation during sedation protocols can be guided through several awakening tools that are reliable for monitoring the level of sedation in neurocritical care units and neurological response. One commonly used test is the Richmond Agitation-Sedation Scale (RASS), which evaluates the patient's agitation and sedation state [57, 58]. It ranges from + 4 (combative) to -5 (unarousable) and has been implemented in several critical conditions with high predictive accuracy [57–59]. Other sedation assessment tools such as the Ramsay Sedation Scale (RSS), or Sedation Agitation Scale (SAS) have been developed and tested, showing varying levels of validity and reliability, and some of them employ similar numerical references [56]. Additionally, physiologic sedation-assessment tools like the Bispectral Index (BIS), and the Patient State Index (PSI) monitoring systems which are based on the processed electroencephalogram or evoked potentials have been implemented with promising results [60, 61].

Heavner et al. conducted a systematic review and metanalysis including studies that appraise the strength of correlation between concurrent assessments of BIS and Richmond Agitation Sedation Scale (RASS), Ramsay Sedation Scale (RSS), or Sedation Agitation Scale (SAS) in critically ill adult patients [61]. The analysis encompassed twenty-four studies with a total of 1235 patients and the association between BIS and RASS, RSS, and SAS overall was 0.68 (95% confidence interval, 0.61–0.74, $T^2 = 0.06$ $I^2 = 71.26\%$) [61]. These results suggest that the BIS is generally well-correlated with the sedation scales RASS, RSS, and SAS. However, there is variability in the strength of this correlation depending on the sedation scale used and the inherent heterogeneity among the studies. While preliminary data for the validity of BIS shows it as a potential measure of sedation intensity when clinical scales cannot be used, its effectiveness may vary depending on the specific sedation scale and patient population being assessed.

Spontaneous awakening protocols such as the wake-up and breath protocol can be used to progressively titrate sedation in patients with extubation criteria and when safety parameters are met [1, 33, 34, 65, 66]. The presence of active seizures, active alcohol withdrawal, use of paralytic agents, active myocardial ischemia, severe hypoxemia requiring high levels of fractional inspired O2, and elevated intracranial pressure may contradict the spontaneous awakening trials [1, 33]. To avoid unnecessary harm and complications derived from this intervention, markers of failure must be recognized and if present, restarting sedatives at 50% of the previous dosage is recommended (Table 2) [1].

Sedation Vacations in Neurocritical Care: Balancing Benefits and Risks

In the era of evidence-based medicine, the decision-making process has shifted from empiric treatments towards accurate therapeutic approaches and specific guidelines [1, 62]. As it has been mentioned before, prolonged sedation protocols have been associated with worse outcomes in critical care. Thus, there is a need to support with more evidence the idea that daily sedation interruption must be implemented with proper precautions. Hume N. et al. carried out a systematic review and meta-analysis to assess the impact of following the Society of Critical Care Medicine clinical practice guidelines addressing recommendations about pain, agitation/sedation, delirium, ICU immobility, and sleep disruption [63, 64]. These guidelines suggest that daily interruption sedation is linked to benefits for patients in the ICU [65, 66]. Similarly, the results of this systematic review support that implementing strategies to adopt the guidelines and recommendations can reduce the duration of mechanical ventilation for both cohort studies and randomized controlled trials, ICU length of stay, and mortality for randomized controlled trials (RR 0.79; 95% CI, 0.71–0.89; $I^2 = 0\%$) [63]. In terms of delirium rates, in either the cohort studies or the randomized controlled trials

Table 2 Parameters for evaluating sedation interruption suitability

Markers of potential harm from spontaneous awakening trials*
Presence of agitation per SAS or RASS scales
Pain
Respiratory rate > 35 bpm
oxygen saturation < 88%
Respiratory distress
Acute cardiac arrhythmia
Safety markers for spontaneous breathing trials
No agitation
Oxygen saturation > 88%
FiO_2 < 50%
PEEP < 8 cm H_2O
No active myocardial ischemia
Minimal vasopressor requirements
Good inspiratory efforts

This table was created based on the recommendations established by Sharma S. et al. *The presence of failure markers for awakening trials indicates the restarting of sedatives at 50% of the previous dosage with a follow-up within 24 h (1)

Bpm Breaths per minute, *FiO_2* Fraction of inspired oxygen, *PEEP* Positive end-expiratory pressure

there was no difference in reduction occurrence. This study has some limitations such as a lack of data on care even after intervention implementation was often reported and adherence to intervention may compromise the certainty of these findings.

From 2020 to 2021 Graham N. et al. evaluate the impact of guidelines for sedation interruptions in patients on mechanical ventilation [67]. By apprising the included studies through the AGREE-III score, the main conclusions of this work were that although sedation interruption is inextricably linked to better outcomes there is a lack of quality of methodological development across all available guidelines containing a recommendation, and the evidence is considered weak.

More recently, Hernandez F. et al. systematic review and metanalysis assessed the role of protocolized sedation in intensive care settings finding that protocolized sedation including daily interruptions demonstrated a reduced RR for mortality (RR: 0.80, 95% CI 0.68–0.93, $p < 0.01$, I2 = 0%) and a decrease in ventilation days (mean difference: − 1.12, 95% CI − 2.11 to − 0.14, $p = 0.03$, I2 = 84%) [64]. There was also a notable reduction in ICU stay (mean difference: − 2.24, 95% CI − 3.59 to − 0.89, $p < 0.01$, I2 = 81%) [64]. In this study, the only parameter that did not show a significant difference was the incidence of self-extubation.

Besides the evident decrease in ICU stays and time on mechanical ventilation, daily sedation interruption has been shown to foster the ability to accurately adjust sedation, which lowers the risk of ventilator-associated lung infections and reduces the need for neurological diagnostic tests related to oversedation [1, 68] (Fig. 1). In 2016 a clinical randomized trial was conducted on 80 patients with intravenous sedation infusion who were allocated to a daily sedation vacation protocol instead of the routine sedation vacation to understand the effect of daily sedation interruption protocol on the incidence of ventilator-associated pneumonia (VAP). The daily sedation interruption group experienced a significantly lower incidence of VAP compared to the control group ($P < 0.05$) [68].

The presence of complications derived from vacation sedation is more common in neurological conditions that usually require prolonged sedation to control elevated intracranial pressure [1, 69]. Retrospective cohort studies of patients with aneurysmal subarachnoid hemorrhage suggest that patients who underwent sedation interruption commonly develop higher intracranial pressures with subsequent re-bleedings and delayed cerebral ischemia [69]. Additionally, the inadequate implementation of sedation vacation protocols can lead to anxiety and confusion in patients who don't remember their intubation status and may pull out the endotracheal tube which can harm the laryngeal area and cause respiratory failure [1, 34, 35]. Moreover, the sympathetic hyperreactivity derived from this response leads to hypertension and tachycardia increasing the risk of stroke and acute myocardial infarction [1]. However, there is limited evidence regarding the frequency and associations with these complications and further research is needed.

Discussion

Sedation vacations, whether applied through algorithmic protocols or daily interruption, remains a safe and effective method compared to standard management for ventilated ICU patients. A sedation break is necessary to evaluate the patient's neurological status and determine the need for continued sedation. Evidence-based practice recommends providing this break at least once daily, however, the existing guidelines and recommendations exhibit several deficiencies with evidence of low quality, which compromises the overall credibility and applicability of the recommendations. A Multidisciplinary and tailored independent approach for patients is key to determining whether sedation interruption can be attempted or not. Despite the beneficial effect of sedation interruption, the presence of complications must be addressed accordingly to avoid detrimental outcomes and mortal consequences. Further prospective, controlled studies are needed to identify the most effective strategies to implement these recommendations and to further comprehend the roles of nurses and other essential personnel in these protocols.

Conclusion

Sedation vacations in neurocritical care units play a critical role in optimizing patient outcomes by reducing mechanical ventilation duration, ICU stay length, and mortality rates. However, implementing these protocols requires a multidisciplinary approach and careful consideration of patient-specific factors. Continued research is essential to refine these strategies and improve guideline quality, ensuring safe and effective sedation management in critically ill neurological patients.

Author Contributions All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by J.S.R.B., L.R.M.S., T.J. The first draft of the manuscript was written J.S.R.B. and all authors commented on previous versions of the manuscript. L.R.M.S., T.J. prepared the tables, and J.S.R.B. prepared the figures. All authors read and approved the final manuscript.

Funding The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

1. Sharma S, Hashmi MF, Valentino III DJ. Sedation Vacation in the ICU. [Updated 2024 Jan 9]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK513327/. Accessed 21 May 2024.
2. Pettit NR, Wood T, Lieber M, O'Mara MS. Intensive care unit design and mortality in trauma patients. J Surg Res. 2014;190(2):640–6. https://doi.org/10.1016/j.jss.2014.04.007.
3. Orban J-C, Walrave Y, et al. Causes and characteristics of death in Intensive Care Units. Anesthesiology. 2017;126(5):882–9. https://doi.org/10.1097/aln.0000000000001612.
4. Jianhua Y, Xingxing S, Fen W, Xijing Z. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue*. 2015;27(11):880-884.
5. Mayr VD, Dünser MW, Greil V, et al. Causes of death and determinants of outcome in critically ill patients. Crit Care. 2006;10(6):R154. https://doi.org/10.1186/cc5086.
6. Mendez MP, Lazar MH, Digiovine B, et al. Dedicated multidisciplinary ventilator bundle team and compliance with sedation vacation. Am J Crit Care. 2013;22(1):54–60. https://doi.org/10.4037/ajcc2013873.
7. Stollings JL, Balas MC, Chanques G. Evolution of sedation management in the intensive care unit (ICU). Intensive Care Med. 2022;48:1625–8. https://doi.org/10.1007/s00134-022-06806-x.
8. Kress JP, Pohlman AS, O'Connor MF, et al. Daily Interruption of Sedative Infusions in Critically Ill Patients Undergoing Mechanical Ventilation. N Engl J Med. 2000;342(20):1471–7. https://doi.org/10.1056/NEJM200005183422002.
9. Mogensen FL-H, Delle C, Nedergaard M. The Glymphatic System (En)during Inflammation. Int J Mol Sci. 2021;22(14):7491. https://doi.org/10.3390/ijms22147491.
10. Moscote-Salazar LR, Beltran-Ruiz JJ, Reyes-Bello JS, Restrepo-Lugo CM. Pathobiology of the Glymphatic System in the Traumatic Brain Injury: A Narrative Review. Panam J Trauma, Crit Care Emerg Surg. 2022;11(2):82–7. https://doi.org/10.5005/jp-journals-10030-1389.
11. Balança B, Desmurs L, Grelier J, Perret-Liaudet A, Lukaszewicz AC. DAMPs and RAGE Pathophysiology at the Acute Phase of Brain Injury: An Overview. Int J Mol Sci. 2021;22(5):2439. https://doi.org/10.3390/ijms22052439.
12. Gerber KS, Alvarez G, Alamian A, Behar-Zusman V, Downs CA. Biomarkers of Neuroinflammation in Traumatic Brain Injury. Clin Nurs Res. 2022;31(7):1203–18. https://doi.org/10.1177/10547738221107081.
13. Ferrara M, Bertozzi G, Volonnino G, Di Fazio N, Frati P, Cipolloni L, La Russa R, Fineschi V. Glymphatic System a Window on TBI Pathophysiology: A Systematic Review. Int J Mol Sci. 2022;23(16):9138. https://doi.org/10.3390/ijms23169138.
14. Thrane AS, Rangroo Thrane V, Nedergaard M. Drowning stars: Reassessing the role of astrocytes in brain edema. Trends Neurosci. 2014;37(11):620–8. https://doi.org/10.1016/j.tins.2014.08.010.
15. Maslonka MA, Sheehan KN, Datar SV, Vachharajani V, Namen A. Pathophysiology and Management of Neurogenic Pulmonary Edema in Patients with Acute Severe Brain Injury. South Med J. 2022;115(10):784–9. https://doi.org/10.14423/SMJ.0000000000001457.
16. Ziaka M, Exadaktylos A. Pathophysiology of acute lung injury in patients with acute brain injury: the triple-hit hypothesis. Crit Care. 2024;28(1):71. https://doi.org/10.1186/s13054-024-04855-w.
17. Robba C, Bonatti G, Pelosi P, et al. Extracranial complications after traumatic brain injury: targeting the brain and the body. Current Opinion in Critical Care. 2020;26(2):137–46. https://doi.org/10.1097/MCC.0000000000000707.
18. Ziaka M, Exadaktylos A. Brain-lung interactions and mechanical ventilation in patients with isolated brain injury. Crit Care. 2021;25(1):358. https://doi.org/10.1186/s13054-021-03778-0.
19. Mukherjee S, Hanidziar D. More of the Gut in the Lung: How Two Microbiomes Meet in ARDS. Yale J Biol Med. 2018;91(2):143–9.
20. Siwicka-Gieroba D, Terpilowska S, Robba C, Kotfis K, Wojcik-Zaluska A, Dabrowski W. Concentration of Apoptotic Factors in Bronchoalveolar Lavage Fluid, as Potential Brain-Lung Oxygen Relationship, Correspond to the Severity of Brain Injury. J Integr Neurosci. 2023;22(2):49. https://doi.org/10.31083/j.jin2202049.
21. Banerjee A, Mohapatra S, McCullough LD. Stroke and the Microbiome. Stroke. 2024;55(3):762–4. https://doi.org/10.1161/STROKEAHA.123.044249.
22. Benakis C, Brea D, Caballero S, et al. Commensal microbiota affects ischemic stroke outcome by regulating intestinal γδ T cells. Nat Med. 2016;22(5):516–23. https://doi.org/10.1038/nm.4068.
23. Krakovski MA, Arora N, Jain S, et al. Diet-microbiome-gut-brain nexus in acute and chronic brain injury. Front Neurosci. 2022;16:1002266. https://doi.org/10.3389/fnins.2022.1002266.
24. Kramer AH, Zygun DA. Do Neurocritical Care Units Save Lives? Measuring The Impact of Specialized ICUs. Neurocrit Care. 2011;14:329–33. https://doi.org/10.1007/s12028-011-9530-y.
25. Goodman DJ, Kumar MA. Evidence-based neurocritical care. Neurohospitalist. 2014;4(2):102–8. https://doi.org/10.1177/1941874413507928.

26. Finley Caulfield A, Mlynash M, Eyngorn I, et al. Prognostication of ICU Patients by Providers with and without Neurocritical Care Training. Neurocrit Care. 2022;37(1):190–9. https://doi.org/10.1007/s12028-022-01467-6.
27. Pham X, Ray J, Neto AS, et al. Association of Neurocritical Care Services With Mortality and Functional Outcomes for Adults With Brain Injury: A Systematic Review and Meta-analysis. JAMA Neurol. 2022;79(10):1049–58. https://doi.org/10.1001/jamaneurol.2022.2456.
28. Yan A, Torpey A, Morrisroe E, Andraous W, Costa A, Bergese S. Clinical Management in Traumatic Brain Injury. Biomedicines. 2024;12(4):781. https://doi.org/10.3390/biomedicines12040781.
29. Hawryluk GWJ, Citerio G, Hutchinson P, et al. Intracranial pressure: current perspectives on physiology and monitoring [published correction appears in Intensive Care Med. 2023 Mar;49(3):384]. Intensive Care Med. 2022;48(10):1471–1481. https://doi.org/10.1007/s00134-022-06786-y.
30. Laws JC, Vance EH, Betters KA, et al. Acute Effects of Ketamine on Intracranial Pressure in Children With Severe Traumatic Brain Injury. Crit Care Med. 2023;51(5):563–72. https://doi.org/10.1097/CCM.0000000000005806.
31. Ammar A, Ammar MA, Tesoro EP. Neuropharmacology in the Intensive Care Unit. Crit Care Clin. 2023;39(1):171–213. https://doi.org/10.1016/j.ccc.2022.07.007.
32. Opdenakker O, Vanstraelen A, De Sloovere V, Meyfroidt G. Sedatives in neurocritical care: an update on pharmacological agents and modes of sedation. Curr Opin Crit Care. 2019;25(2):97–104. https://doi.org/10.1097/MCC.0000000000000592.
33. Bureau C, Demoule A. Weaning from mechanical ventilation in neurocritical care. Rev Neurol (Paris). 2022;178(1–2):111–20. https://doi.org/10.1016/j.neurol.2021.08.005.
34. Bauerschmidt A, Al-Bermani T, Ali S, et al. Modern Sedation and Analgesia Strategies in Neurocritical Care. Curr Neurol Neurosci Rep. 2023;23(4):149–58. https://doi.org/10.1007/s11910-023-01261-7.
35. Prabhakar H, Tripathy S, Gupta N, et al. Consensus Statement on Analgo-sedation in Neurocritical Care and Review of Literature. Indian J Crit Care Med. 2021;25(2):126–33. https://doi.org/10.5005/jp-journals-10071-23712.
36. Mahajan S, Sharma T, Panda NB, et al. Comparison of propofol and desflurane for postoperative neurocognitive function in patients with aneurysmal subarachnoid hemorrhage: A prospective randomized trial. Surg Neurol Int. 2024;15:84. https://doi.org/10.25259/SNI_788_2023.
37. Syeda S, Bansal S, Chakrabarti D, Bhadrinarayan V. The requirement of propofol for induction of anesthesia in patients with traumatic brain injury determined using bilateral bispectral index and target controlled infusion - An observational cohort study. J Anaesthesiol Clin Pharmacol. 2023;39(2):208–14. https://doi.org/10.4103/joacp.joacp_216_21.
38. Van S, Lam V, Patel K, Humphries A, Siddiqi J. Propofol-Related Infusion Syndrome: A Bibliometric Analysis of the 100 Most-Cited Articles. Cureus. 2023;15(10):e46497. https://doi.org/10.7759/cureus.46497.
39. Russo G, Harrois A, Anstey J, et al. Early sedation in traumatic brain injury: a multicentre international observational study. Crit Care Resusc. 2023;24(4):319–29. https://doi.org/10.51893/2022.4.OA2.
40. Beniwal M, Muthuchellappan R, Vazhayil V, et al. Does Propofol Effect Site (Brain) Concentration Predicted by Target-Controlled Infusion Correlate with Propofol Measured in the Brain? An Exploratory Study in Neurosurgical Patients. World Neurosurg. 2023;179:e15–20. https://doi.org/10.1016/j.wneu.2023.06.032.
41. Dittrich TD, Vock D, Fisch U, et al. Efficacy and Tolerability of Intranasal Midazolam Administration for Antiseizure Treatment in Adults: A Systematic Review. Neurocrit Care. https://doi.org/10.1007/s12028-024-01971-x.
42. Chiu WT, Campozano V, Schiefecker A, et al. Management of Refractory Status Epilepticus: An International Cohort Study (MORSE CODe) Analysis of Patients Managed in the ICU. Neurology. 2022;99(11):e1191–201. https://doi.org/10.1212/WNL.0000000000200818.
43. Escamilla-Ocañas CE, Albores-Ibarra N. Current status and outlook for the management of intracranial hypertension after traumatic brain injury: decompressive craniectomy, therapeutic hypothermia, and barbiturates. Neurologia (Engl Ed). 2023;38(5):357–63. https://doi.org/10.1016/j.nrleng.2020.08.024.
44. Carney, Nancy PhD; Totten, Annette M. PhD; O'Reilly, Cindy BS; Ullman, Jamie S. MD; Hawryluk, Gregory W.J. MD, PhD; Bell, Michael J. MD; Bratton, Susan L. MD; Chesnut, Randall MD; Harris, Odette A. MD, MPH; Kissoon, Niranjan MD; Rubiano, Andres M. MD; Shutter, Lori MD; Tasker, Robert C. MBBS, MD; Vavilala, Monica S. MD; Wilberger, Jack MD; Wright, David W. MD; Ghajar, Jamshid MD, PhD. Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. Neurosurgery. 2017:80(1):6–15. https://doi.org/10.1227/NEU.0000000000001432.
45. Bui VT, Pfeifer C, Snelgrove DK, Neyens RR. Pain Assessment Following Opioid Administration in Aneurysmal Subarachnoid Hemorrhage Associated Headache. J Pharm Pract. https://doi.org/10.1177/08971900241248481.
46. Liu SY, Kelly-Hedrick M, Temkin N, et al. Association of Early Dexmedetomidine Utilization With Clinical and Functional Outcomes Following Moderate-Severe Traumatic Brain Injury: A Transforming Clinical Research and Knowledge in Traumatic Brain Injury Study. Crit Care Med. 2024;52(4):607–17. https://doi.org/10.1097/CCM.0000000000006106.
47. Kimmons LA, Alzayadneh M, Metter EJ, Alsherbini K. Safety and Efficacy of Ketamine Without Intubation in the Management of Refractory Seizures: A Case Series. Neurocrit Care. 2024;40(2):689–97. https://doi.org/10.1007/s12028-023-01811-4.
48. Tantillo G, Davis N, Granstein J, et al. Provider Experience With the Use of Ketamine for Refractory Status Epilepticus. Clin Neuropharmacol. 2024;47(2):37–43. https://doi.org/10.1097/WNF.0000000000000582.
49. Loi MV, Lee JH, Huh JW, et al. Ketamine Use in the Intubation of Critically Ill Children with Neurological Indications: A Multicenter Retrospective Analysis. Neurocrit Care. 2024;40(1):205–14. https://doi.org/10.1007/s12028-023-01734-0.
50. Sethuraman M, Bidkar PU, Mariappan R, Deopujari RC, Vanamoorthy P, Massand M. Recent advancements in the practice of neuroanaesthesia and neurocritical care: An update. Indian J Anaesth. 2023;67(1):85–90. https://doi.org/10.4103/ija.ija_949_22.
51. Ditz C, Baars H, Schacht H, et al. Volatile Sedation With Isoflurane in Neurocritical Care Patients After Poor-grade Aneurysmal Subarachnoid Hemorrhage. World Neurosurg. 2023;173:e194–206. https://doi.org/10.1016/j.wneu.2023.02.032.
52. Wieruszewski ED, ElSaban M, Wieruszewski PM, Smischney NJ. Inhaled volatile anesthetics in the intensive care unit. World J Crit Care Med. 2024;13(1):90746. https://doi.org/10.5492/wjccm.v13.i1.90746.PMID:38633473;PMCID:PMC11019627.
53. Wijdicks EFM. Clinical observations in acute neurology: A historical explanation of the present. Eur J Neurol. https://doi.org/10.1111/ene.16241.
54. López de Audícana-Jimenez de Aberasturi Y, Vallejo-De la Cueva A, Aretxabala-Cortajarena N, et al. The pupillary dilation reflex to a nociceptive stimulus as a tool for analgesia management: A diagnostic study. Aust Crit Care. 2024;37(2):230–235. https://doi.org/10.1016/j.aucc.2023.06.009.
55. Favre E, Rahmaty Z, Ben-Hamouda N, et al. Nociception assessment with videopupillometry in deeply sedated intensive care patients: Discriminative and criterion validations. Aust Crit Care. 2024;37(1):84–90. https://doi.org/10.1016/j.aucc.2023.07.038.

56. Olson DM, Phillips K, Graffagnino C. Toward Solving the Sedation-Assessment Conundrum: Neurofunction Monitoring. Crit Care Nurs Clin North Am. 2016;28(2):205–16. https://doi.org/10.1016/j.cnc.2016.02.007.
57. Medlej K. Calculated decisions: Richmond Agitation-Sedation Scale (RASS). Emerg Med Pract. 2021;23(Suppl 3):CD3–4.
58. Harsha MS, Bhatia PK, Sharma A, Sethi P. Comparison of Quantium Consciousness Index and Richmond Agitation Sedation Scale in Mechanically Ventilated Critically Ill Patients: An Observational Study. Indian J Crit Care Med. 2022;26(4):491–5. https://doi.org/10.5005/jp-journals-10071-24183.
59. Rakhit S, Wang L, Lindsell CJ, et al. Multicenter International Cohort Validation of a Modified Sequential Organ Failure Assessment Score Using the Richmond Agitation-sedation Scale. Ann Surg. 2022;276(2):e114–9. https://doi.org/10.1097/SLA.0000000000004484.
60. Mathur S, Patel J, Goldstein S, Hendrix JM, Jain A. Bispectral Index. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; 2023.
61. Heavner MS, Gorman EF, Linn DD, Yeung SYA, Miano TA. Systematic review and meta-analysis of the correlation between bispectral index (BIS) and clinical sedation scales: Toward defining the role of BIS in critically ill patients. Pharmacotherapy. 2022;42(8):667–76. https://doi.org/10.1002/phar.2712.
62. Louie JM, Lonardo NW, Mone MC, Stevens VW, Deka R, Shipley W, Barton RG. Outcomes When Using Adjunct Dexmedetomidine with Propofol Sedation in Mechanically Ventilated Surgical Intensive Care Patients. Pharmacy (Basel). 2018;6(3):93. https://doi.org/10.3390/pharmacy6030093.PMID:30154389;PMCID:PMC6164835.
63. Hume NE, Zerfas I, Wong A, Klein-Fedyshin M, Smithburger PL, Buckley MS, Devlin JW, Kane-Gill SL. Clinical Impact of the Implementation Strategies Used to Apply the 2013 Pain, Agitation/Sedation, Delirium or 2018 Pain, Agitation/Sedation, Delirium, Immobility, Sleep Disruption Guideline Recommendations: A Systematic Review and Meta-Analysis. Crit Care Med. 2024;52(4):626–36. https://doi.org/10.1097/CCM.0000000000006178.
64. Hernandez FLC, Ríos MVS, Bolivar YRC, Sánchez JIA. Optimizing patient outcomes: a comprehensive evaluation of protocolized sedation in intensive care settings: a systematic review and meta-analysis. Eur J Med Res. 2024;29(1):255. https://doi.org/10.1186/s40001-024-01839-y.
65. Barr J, Fraser GL, Puntillo K, Ely EW, Gélinas C, Dasta JF, Davidson JE, Devlin JW, Kress JP, Joffe AM, Coursin DB, Herr DL, Tung A, Robinson BR, Fontaine DK, Ramsay MA, Riker RR, Sessler CN, Pun B, Skrobik Y, Jaeschke R; American College of Critical Care Medicine. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med. 2013;41(1):263–306. https://doi.org/10.1097/CCM.0b013e3182783b72.
66. Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJC, Pandharipande PP, Watson PL, Weinhouse GL, Nunnally ME, Rochwerg B, Balas MC, van den Boogaard M, Bosma KJ, Brummel NE, Chanques G, Denehy L, Drouot X, Fraser GL, Harris JE, Joffe AM, Kho ME, Kress JP, Lanphere JA, McKinley S, Neufeld KJ, Pisani MA, Payen JF, Pun BT, Puntillo KA, Riker RR, Robinson BRH, Shehabi Y, Szumita PM, Winkelman C, Centofanti JE, Price C, Nikayin S, Misak CJ, Flood PD, Kiedrowski K, Alhazzani W. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. Crit Care Med. 2018;46(9):e825–73. https://doi.org/10.1097/CCM.0000000000003299.
67. Graham ND, Graham ID, Vanderspank-Wright B, Varin MD, Nadalin Penno L, Fergusson DA, Squires JE. A systematic review and critical appraisal of guidelines and their recommendations for sedation interruptions in adult mechanically ventilated patients. Aust Crit Care. 2023;36(5):889–901. https://doi.org/10.1016/j.aucc.2022.10.011.
68. Shahabi M, Yousefi H, Yazdannik AR, Alikiaii B. The effect of daily sedation interruption protocol on early incidence of ventilator-associated pneumonia among patients hospitalized in critical care units receiving mechanical ventilation. Iran J Nurs Midwifery Res. 2016;21(5):541–6. https://doi.org/10.4103/1735-9066.193420.
69. Schmidbauer ML, Läufer S, Maskos A, Dimitriadis K. Risk factors and outcomes after interruption of sedation in subarachnoid hemorrhage (ROUTINE-SAH)-a retrospective cohort study. Front Neurol. 2024;13(15):1363107. https://doi.org/10.3389/fneur.2024.1363107.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.